National Toxicology Program

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Draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy

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1.0 EXECUTIVE SUMMARY

Background and Objectives

Each year, approximately 1 in 6000 to 1 in 1000 women are diagnosed with cancer during pregnancy (Haas 1984, Smith *et al.* 2003). The frequency is expected to increase as women postpone having children to later ages. Both the disease itself and the modalities available to treat it can pose risks to the health and survival of the woman. If the pregnancy is continued, the cancer patient and her clinicians are faced with the challenge of choosing a course of treatment that is optimal for the mother's health and minimizes the risk of potential harm to the unborn baby. Treatment most often involves some form of chemotherapy and nearly all chemotherapeutic agents are FDA Pregnancy Category D[1], i.e, *investigational or post-marketing data show risk to the fetus.* The evidence of risk of the chemotherapeutic agents usually comes from studies in laboratory animals.

The current medical paradigm for treatment of the pregnant cancer patient is to avoid, whenever possible, administration of cancer chemotherapy during the first trimester due to the vulnerability of organogenesis to chemical perturbation. Exposure during the second and/or third trimester is thought to pose less risk of adverse developmental effects, but may lead to pregnancy complications (Azim *et al.* 2010, Buekers and Lallas 1998, Loibl 2007, Loibl *et al.* 2006, Rizack *et al.* 2009).

The patient diagnosed with cancer during pregnancy and her medical team must make difficult choices regarding the use of chemotherapeutic treatment for cancer in the face of considerable uncertainty. The majority of human studies available to help guide decision-making are case reports and case series, which are generally accepted as the weakest type of epidemiological evidence upon which to reach conclusions. Nevertheless, these data are what is currently available due to the rarity of cancer during pregnancy and the current lack of published prospective research trials on the effects of cancer chemotherapy on pregnancy outcome. In addition, most therapeutic protocols involve treating patients with combinations of chemotherapy agents. Thus, reaching conclusions on any specific agent is challenging.

The overall goal of this NTP monograph is to summarize the reports of effects of gestational exposure to cancer chemotherapy on pregnancy outcomes from these studies and identify the limitations of this information with respect to providing physicians and their patients with information to help make clinical decisions.

The specific objectives of this NTP monograph are to:

1. Review the published data on pregnancy outcomes of women administered cancer chemotherapy during pregnancy and evaluate whether major congenital malformations occur a) at a higher apparent[2] rate than in the prevalence in the general population and b) at a higher

[1] See full descriptions of pregnancy categories A, B, C, D, X at this site (accessed April 1, 2010). http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57

[2] Apparent rate of occurrence are the incidence of developmental effects or pregnancy outcomes in the studies considered in this evaluation (e.g., conceptuses with malformation/total conceptuses).

apparent rate following exposure in the first trimester versus exposure during the second and/or third trimester only.

2. Summarize reports of the effects of cancer chemotherapy on early and late spontaneous fetal loss and pregnancy complications (e.g., intrauterine growth restriction, reduction in fetal amniotic fluid, fetal cardiotoxicity and spontaneous preterm labor).

3. Evaluate the effects of cancer chemotherapy on newborn weight and health, and infant growth and development at follow up.

In an effort to put these effects in context, this NTP monograph also provides background information on the individual cancer chemotherapeutic agents and a brief review of the prevalence and prognosis of seven frequently diagnosed cancers in women during pregnancy. In particular, the evaluation reviews the mechanism of action, indications, evidence of transfer to fetus or breast milk, and developmental toxicity in laboratory animal studies for each cancer chemotherapy agent. The seven cancers frequently diagnosed in patients during pregnancy reviewed in the monograph are: breast cancer, cervical cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, ovarian cancer, and melanoma. The monograph also includes the currently recommended cancer chemotherapy treatment of these cancers.

Methods

The literature search on the topic of cancer and chemotherapy during pregnancy was designed to focus on four key concepts: chemotherapy, pregnancy, pregnancy outcomes, and human studies. The literature search yielded 1310 relevant publications. Of the relevant publications, 436 reported data on one or more female cancer patients treated with cancer chemotherapeutic agents during the pregnancy and the pregnancy outcome. Following exclusion of studies with incomplete data on maternal chemotherapy treatment during pregnancy and/or pregnancy outcomes as well as duplicate reporting of cases, there were 420 publications presenting data on a total of 1190 female cancer patients treated with chemotherapy during pregnancy exposed collectively to a total of 51 cancer chemotherapeutic agents. Data were organized into tables, and text summaries were written for each individual cancer chemotherapeutic agent, which included cases exposed to the agent alone or, more commonly, in combination with other cancer chemotherapeutic agents (see NTP Monograph Sections 5.1-5.32, Appendix C Tables 1 to 32). For agents with 10 or fewer cases, the data were organized into tables only (Appendix D Table 1 to 20). The draft NTP Monograph identifies a drug by its common name, not by its brand name, so there may be more than one manufacturer for a drug.

In addition to summarizing the data from human studies, the text also reviewed information on each cancer chemotherapeutic agent regarding: mechanism of action, route of administration, indications, placental or breast milk transport, and developmental toxicity studies in animals. The NTP monograph also reviewed primary and secondary literature on seven of the cancer types frequently diagnosed during pregnancy. This section on the seven tumor types reviewed the definition and occurrence of each cancer type, the impact of pregnancy on the prognosis of each cancer type, the current cancer chemotherapy regimen used to treat each cancer type, and provides a summary table of the number of reported cases treated with each chemotherapeutic agent. The background information on the chemotherapy agents and seven of the frequently diagnosed cancers during pregnancy is drawn from the most current literature available in order to provide context for the topic of pregnancy outcomes following cancer chemotherapy during pregnancy, but is not intended to be an exhaustive review of these topics.

The human data were identified as apparent rates of occurrence major congenital malformations, fetal loss, pregnancy complications and outcomes, and growth and development of offspring exposed in utero to cancer chemotherapy; these apparent rates of occurrence may or may not reflect the actual, exact rates of occurrence for the population. Apparent rates of occurrence were evaluated across all studies for any exposure to chemotherapy, and also compared across the individual chemotherapeutic agents (administered either singly or in combination) to identify those agents that may be more often associated with an adverse health outcome. However, statistical comparisons were not undertaken because of the limitations in using this literature base for quantitative analysis; i.e., the majority of these publications were case reports (75.1%; n=313/417 publications and case series (20.9%; n=87/417 publications). The apparent rates of occurrence were also compared to national data; while these comparisons were not statistical analyses, they did provide a point of reference in interpreting the apparent rates of occurrence. Greater confidence was placed on data for individual agents for which there were more human data; e.g, cyclophosphamide and cytarabine were among the agents that were more frequently used during pregnancy in the literature with 397 and 149 conceptuses exposed, respectively. It is possible that data from largely case reports and registries of cancer during pregnancy may be influenced by publication bias as adverse pregnancy outcomes are more likely to be reported, while normal pregnancy outcomes may be less likely to be published. It is also possible that the apparent rates of occurrence from the published studies may underreport the population incidence of adverse developmental effect; i.e., early pregnancy loss of undetected malformed conceptuses may reduce the incidence of malformations.

Results

In total, the NTP monograph compiled data on 1190 female cancer patients treated with chemotherapy during pregnancy; these patients had 1201 pregnancies and 1216 conceptuses. These patients were treated collectively to 51 cancer chemotherapeutic agents during pregnancy. Of the 32 chemotherapeutic agents with reports of more than 10 cases, 29 agents are considered to be human embryotoxicants and/or teratogens (FDA Pregnancy Category D, n=28 agents or X, n=1 agent (methotrexate)), and three agents (dacarbazine, interferon alpha, and rituximab) are known or possible animal embryotoxicants or teratogens (FDA Category C).

The NTP monograph addressed the following questions:

1. <u>Are major congenital malformations more frequently associated with exposure to cancer chemotherapy use in the first trimester versus the second and/or third trimester only?</u> Major congenital malformations were more frequently observed in conceptuses exposed to cancer chemotherapy during the first trimester than in conceptuses exposed to cancer chemotherapy in the second and/or third trimester only (Figure 1); these data were consistent with the current medical opinion that the first trimester is more sensitive to chemical perturbation than the second and/or third trimester. Of the 1216 conceptuses evaluated in this monograph, the occurrence of major malformations was 10.4% (43/412 conceptuses) following exposure to any cancer chemotherapy during the first trimester relative to the 2.9% occurrence (22/767 conceptuses) of major malformations following exposure during the second and/or third trimester only; timing of exposure was not specified for 37 conceptuses (none were malformed).

As a point of comparison, the prevalence of major congenital malformations in the general population of the United States is about 3% (Correa *et al.* 2007). While targeted therapies (i.e., all-trans retinoic acid, rituximab, interferon alpha, tamoxifen, imatinib, and trastuzumab) have fewer adverse side effects in cancer patients, the malformation rate following first trimester exposure to these agents was comparable to the apparent malformation rate of all cancer chemotherapeutics combined (8.5%). The malformation rates following first trimester exposure for rituximab, imatinib and tamoxifen were 16.7% (1/6 conceptuses), 8.7% (13/149 conceptuses), and 27.3 % (3/11 conceptuses). In contrast, there were no reported malformations following first trimester exposure for all-trans retinoic acid (n=5 conceptuses), interferon (n=21 conceptuses) or trastuzumab (n=14 conceptuses).

2. <u>Is cancer chemotherapy use during pregnancy associated with fetal loss and pregnancy complications?</u> The apparent rate of late spontaneous fetal death (>22 weeks of gestation) following in utero exposure to any cancer chemotherapy (1.6%; 22/1216 conceptuses) was slightly higher than rates of late spontaneous fetal loss for the general population in the US from 1990 to 2004 (0.3 to 0.4%) (MacDorman 2005, Martin 2011). Regarding specific cancer chemotherapeutic agents, late spontaneous fetal loss (>22weeks of gestation to birth) appeared to occur more frequently following exposure individually or in combination therapy to cytarabine (7.5%; 9/120 conceptuses), 6-thioguanine (9.3%; 4/43 conceptuses), and daunorubicin (11%; 9/82 conceptuses) (Table 2). In contrast, the apparent rate of early spontaneous pregnancy loss (≤22 weeks of gestation) following in utero exposure to any cancer chemotherapy (3.8%; 46/1216 conceptuses) appeared to be lower than a pooled estimate of spontaneous abortion in healthy women of 13% (95% CI = 10% to 16%) (Wilcox 2010). When observed by individual agent, spontaneous abortions occurred at an apparent mean rate of 9.7% (range of 2.5% to 16.1%; (Table 1) following in utero exposure to cancer chemotherapeutic agents for which data on 20 or more conceptuses were reported.

   The maintenance of amniotic fluid levels and cardiac function appear to be two endpoints that are adversely affected by the administration of specific cancer chemotherapeutic agents during pregnancy. Trastuzmab, a monoclonal antibody to the human epidermal growth factor receptor 2 (HER2) which blocks tyrosine kinase activation, caused moderate to severe reductions in amniotic fluid when administered during the second and/or third trimester of pregnancy. A reduction in amniotic fluid occurred in 11 of 13 pregnancies (84.6%) exposed to trastuzumab during the second and/or third trimester (Table 2). This apparent rate of occurrence of oligohydramnios is higher than the prevalence in the general population, which is reported to occur at a rate of 2.3 to 4% of all pregnancies (March of Dimes 2010). In two cases, severe reduction in amniotic fluid appeared to be associated with fetal and/or infant renal failure (Beale *et al.* 2009, Warraich and Smith 2009). This effect appears to be reversible, if administration of the agent is stopped. Regarding fetal cardiotoxicity, there was concern that anthracycline antibiotics (i.e., doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone) might cause fetal cardiotoxicity based on known adverse cardiac side effects in patients administered these agents (AAP Pharmaceuticals 2010, Gilead Sciences 2002, Mayne 2006, Pharmacia & UpJohn Company 2010, Teva 2009). Fetal cardiac effects occurred in three of 23 pregnancies exposed to idarubicin (Claahsen *et al.* 1998, Yucebilgin *et al.* 2004) and 3 of 17 pregnancies exposed to mitoxantrone (Garcia *et al.* 1999, Mavrommatis *et al.* 1998), including one pregnancy exposed to both of these agents (Baumgartner *et al.* 2009); however, no fetal cardiotoxicity was reported following gestational exposure to daunorubicin (n=104 conceptuses), doxorubicin (n=411 conceptuses), or epirubicin (n=72 conceptuses). Van

Calsteren et al. (2006) conducted a prospective study evaluating the cardiac morphology and function of children gestationally exposed to cancer chemotherapy at four Belgian medical centers. They reported no differences in cardiological outcome at age 2 months to 66 months: however, a trend for reduced left ventricular mass and heart wall thickness was observed in the seven children exposed in utero to anthracycline antibiotics.

3. Is cancer chemotherapy use during pregnancy associated with small for gestational age newborns? The frequency of small for gestational age infants at birth appears to be similar or slightly higher following in utero exposure to certain chemotherapeutics agents compared to the general population of North America. For cancer chemotherapeutic agents with more data, small for gestational age newborns occurred at a rate of 16.5% (22/133 infants), 18.4% (16/87 infants), 12.7% (14/110 infants) and 10.3% (12/116 infants) following in utero exposure to cyclophosphamide, cytarabine, doxorubicin, and vincristine, respectively (Table 3). As a point of comparison, the incidence of small for gestational age newborns in the general population was 8.3% for data collected from 1999-2003 in Quebec, Canada (Auger *et al.* 2009). In a registry survey of 210 women diagnosed with cancer during pregnancy, the frequency of small for gestational age was similar between the infants exposed to cancer chemotherapy in utero and infants not exposed to cancer chemotherapy in utero: exposed = 7.7% (12/157 infants) and non-exposed = 7.1% (5/70 infants) (Cardonick *et al.* 2010).

4. Is cancer chemotherapy use during pregnancy associated with adverse health effects in newborns? Transient myelosuppression was observed in 50 of 1061 newborns exposed to cancer chemotherapy near or at the time of birth in publications reviewed in the NTP monograph. For example, transient myelosuppression occurred in infants exposed in utero to cyclophosphamide (4.8%; 18/378 infants), cytarabine (9.2%; 11/120 infants), and doxorubicin (2.2%; 9/402 infants). It has been suggested that transient myelosuppression may be avoided if administration of cancer chemotherapy is halted three weeks prior to birth (Sorosky *et al.* 1997). However, Aviles et al. (1991) reported that eight of 43 children had pancytopenia at birth, even though their mothers had discontinued cancer chemotherapy three weeks prior to giving birth; this condition resolved within 3 to 10 weeks following birth. In most cases, transient myelosuppression resolved without treatment.

5. Is cancer chemotherapy use during pregnancy associated with adverse effects on growth and development in children? Normal growth and development were reported for a majority of children exposed in utero to cancer chemotherapy. For example, 95% of children exposed in utero to cyclophosphamide had normal growth and development at ages ranging from 6 months to 22 years old (their age at their last follow up evaluation; 276/283 children). There was only one report of a child (a male twin) developing cancer following exposure to cancer chemotherapy; the mother was administered cyclophosphamide during the period of conception and throughout pregnancy, and his female twin had normal growth and development (Zemlickis *et al.* 1993).

Conclusions

In conclusion, administration of cancer chemotherapy during the first trimester of development appears to result a higher apparent rate of occurrence of major congenital malformations compared to exposure in the second and/or third trimester only, as well as to the general United States population. However, when exposure occurs in the second and/or third trimester, proper surveillance of fetal development is necessary as some agents can reduce amniotic fluid levels (i.e., trastuzumab) or induce intrauterine growth restriction. Broader participation in registries of cancer during pregnancy, prospective studies of the pregnancy outcomes of women receiving chemotherapy for cancer treatment, and studies evaluating the likelihood of late onset adverse health outcomes of the children exposed in utero to cancer chemotherapy are needed to more thoroughly assess the risks of gestational exposure to cancer chemotherapy. Ultimately, these data on pregnancy outcomes and development of children exposed in utero to cancer chemotherapy will be useful in the development and continued improvement of consensus guidelines for the diagnosis, staging, and treatment of cancer of pregnant women (Amant *et al.* 2010, Amant *et al.* 2009, Loibl *et al.* 2006, Morice *et al.* 2009).

Table 1 Incidence of spontaneous abortion (early fetal death at ≤22 weeks gestation) and intrauterine fetal death (late spontaneous fetal death at >22 weeks of gestation) following gestational administration of each cancer chemotherapeutic agent (singly or in combination therapy) following exposure during the first trimester, or in the second and/or third trimester only.

	Spontaneous abortion Trimester exposed (affected/total conceptuses)		**Intrauterine fetal death** Trimester exposed (affected/total conceptuses)	
Agent (total conceptuses)[a]	**1st**	**2nd and/or 3rd only**	**1st**	**2nd and/or 3rd only**
5-Fluorouracil (162)	20% (3/15)	0% (0/147)	6.7% (1/15)	0% (0/147)
6-Mercaptopurine (84)	13.2% (5/38)	0% (0/42)	2.6% (1/38)	2.4% (1/42)
6-Thioguanine (49)	16.7% (1/6)	0% (0/43)	0% (0/6)	9.3% (4/43)
Actinomycin (13)	NA[b]	0% (0/13)	NA	0% (0/13)
ATRA (29)	20% (1/5)	0% (0/24)	20% (1/5)	0% (0/24)
Bleomycin (95)	0% (0/15)	0% (0/78)	0% (0/15)	1.3% (1/78)
Busulfan (31)	5% (1/20)	0% (0/5)	0% (0/20)	0% (0/5)
Carboplatin (16)	NA	0% (0/15)	NA	0% (0/15)
Cisplatin (94)	0% (0/4)	1.1% (1/89)	0% (0/4)	1.1% (1/89)
Cyclophosphamide (393)	9.3% (4/43)	0.3% (1/350)	2.3% (1/43)	0.9% (3/350)
Cytarabine (152)	16.1% (5/31)	0.8% (1/120)	3.2% (1/31)	7.5% (9/120)
Dacarbazine (56)	12.5% (1/8)	0% (0/48)	0% (0/8)	2.1 (1/48)
Daunorubicin (104)	22.2% (4/18)	1.2% (1/82)	5.6% (1/18)	11.0% (9/82)
Docetaxel (20)	0% (0/1)	0% (0/18)	0% (0/1)	0% (0/18)
Doxorubicin (414)	4.4% (2/45)	0.3% (1/369)	0% (0/45)	1.4% (5/369)
Epirubicin (72)	28.6% (2/7)	0% (0/60)	0% (0/7)	3.3% (2/60)
Etoposide (42)	0% (0/3)	0% (0/39)	0% (0/3)	5.1% (2/39)
Hydroxyurea (62)	2.5% (1/40)	0% (0/20)	10% (4/40)	0% (0/20)
Idarubicin (23)	0% (0/1)	0% (0/17)	0% (0/1)	11.8% (2/17)
Imatinib (154)	12.8% (19/149)	0% (0/5)	1.3% (2/149)	0% (0/5)
Interferon alpha (41)	0% (0/21)	0% (0/19)	0% (0/21)	0% (0/19)
Methotrexate (82)	13.3% (4/30)	0% (0/52)	3.3% (1/30)	1.9% (1/52)
Mitoxantrone (17)	100% (1/1)	0% (0/13)	0% (0/1)	7.7% (1/13)
Nitrogen mustard (30)	11.8% (2/17)	0% (0/13)	0% (0/17)	0% (0/13)
Paclitaxel (31)	NA	0% (0/31)	NA	0% (0/31)
Procarbazine (31)	5.3% (1/19)	0% (0/12)	0% (0/19)	0% (0/12)
Rituximab (24)	16.7% (1/6)	0% (0/18)	0% (0/6)	11.1% (2/18)
Tamoxifen (13)	0% (0/11)	0% (0/2)	0% (0/11)	0% (0/2)
Trastuzumab (18)	0% (0/14)	0% (0/4)	0% (0/14)	0% (0/4)
Vinblastine (72)	6.3% (1/16)	0% (0/55)	0% (0/16)	1.8% (1/55)
Vincristine (221)	10.3% (6/58)	0.6% (1/163)	3.4% (2/58)	3.7% (6/163)
Vinorelbine (14)	0% (0/1)	0% (0/13)	0% (0/1)	0% (0/13)

[a]Differences between the total conceptuses for each agent and the total conceptuses for fetal loss are due to the cases for which timing of exposure was not specified.
[b]Not applicable.

Table 2 Pregnancy complications following gestational administration of each cancer chemotherapeutic agent (singly or in combination therapy) in the first trimester only, or at any time during pregnancy including the second and/or third trimester.

	Intrauterine growth restriction Trimester exposed (# affected/total pregnancies)		**Absent or reduced amniotic fluid** Trimester exposed (# affected/total pregnancies)	
Agent (total pregnancies)[a]	1st only	2nd and/or 3rd	1st only	2nd and/or 3rd
5-Fluorouracil (161)	0% (0/5)	1.3% (2/156)	0% (0/5)	1.3% (2/156)
6-Mercaptopurine (83)	0% (0/13)	1.5% (1/66)	0% (0/13)	1.5% (1/66)
6-Thioguanine (49)	0% (0/5)	4.5% (2/44)	0% (0/5)	0% (0/44)
Actinomycin D (12)	NA[b]	7.7% (1/13)	NA	7.7% (1/13)
ATRA (28)	0% (0/4)	8.3% (2/24)	0% (0/4)	8.3% (2/24)
Bleomycin (93)	0% (0/14)	7.8% (6/77)	0% (0/14)	2.6% (2/77)
Busulfan (31)	0% (0/9)	0% (0/16)	0% (0/9)	0% (0/16)
Carboplatin (16)	NA	0% (0/15)	NA	0% (0/15)
Cisplatin (92)	0% (0/1)	7.7% (7/90)	0% (0/1)	3.3% (3/90)
Cyclophosphamide (394)	0% (0/29)	1.1% (4/365)	0% (0/29)	1.4% (5/365)
Cytarabine (151)	0% (0/21)	6.9% (9/130)	0% (0/21)	3.8% (5/130)
Dacarbazine (55)	0% (0/7)	4.1% (2/49)	0% (0/7)	0% (0/49)
Daunorubicin (103)	0% (0/17)	8.5% (7/82)	0% (0/17)	4.9% (4/82)
Docetaxel (20)	NA	5.3% (1/19)	NA	10.5% (2/19)
Doxorubicin (411)	0% (0/28)	2.1% (8/383)	0% (0/28)	1.0% (4/383)
Epirubicin (72)	0% (0/6)	1.6% (1/61)	0% (0/6)	0% (0/61)
Etoposide (42)	0% (0/2)	22.5% (9/40)	0% (0/2)	7.5% (3/40)
Hydroxyurea (60)	0% (0/25)	0% (0/35)	0% (0/25)	0% (0/35)
Idarubicin (23)	0% (0/1)	17.6% (3/17)	0% (0/1)	11.8% (2/17)
Imatinib (153)	0% (0/101)	0% (0/52)	0% (0/101)	0% (0/52)
Interferon alpha (39)	0% (0/2)	5.6% (2/36)	0% (0/2)	2.8% (1/36)
Methotrexate (79)	0% (0/16)	3.2% (2/63)	0% (0/16)	1.6% (1/63)
Mitoxantrone (17)	0% (0/1)	23.1% (3/13)	0% (0/1)	7.7% (1/13)
Nitrogen mustard (30)	0% (0/15)	0% (0/15)	0% (0/15)	0% (0/15)
Paclitaxel (30)	NA	0% (0/30)	NA	6.7% (2/30)
Procarbazine (31)	0% (0/17)	0% (0/14)	0% (0/17)	0% (0/14)
Rituximab (24)	0% (0/5)	5.3% (1/19)	0% (0/5)	5.3% (1/19)
Tamoxifen (12)	0% (0/3)	0% (0/9)	0% (0/3)	22.2% (2/9)
Trastuzumab (17)	0% (0/4)	84.6% (2/13)	0% (0/4)	84.6% (11/13)
Vinblastine (72)	0% (0/13)	3.5% (2/57)	0% (0/13)	1.8% (1/57)
Vincristine (219)	0% (0/42)	2.3% (4/175)	0% (0/42)	1.7% (3/175)
Vinorelbine (14)	NA	0% (0/14)	NA	7.1% (1/14)

[a] Differences between the total pregnancies for each agent and the total pregnancies for each pregnancy complication are due to the cases for which timing of exposure was not specified.
[b] NA= not applicable.

Table 3 Incidence of spontaneous preterm labor, preterm birth (<37 weeks of gestation), and small for gestational age infants (<10th percentile for body weight) following gestational administration of each cancer chemotherapeutic agent (singly or in combination therapy) at any time during pregnancy.

Agent (total pregnancies[a], total infants)	Spontaneous preterm labor[b] (affected/total pregnancies)	Preterm birth[c, d] (affected/ total infants)	Small for gestational age[d] (affected/total infants)
5-Fluorouracil (161, 162)	3.1% (5/161)	73.3% (33/45)	27.6% (8/29)
6-Mercaptopurine (83, 84)	15.7% (13/83)	53.4% (31/58)	16.3% (7/43)
6-Thioguanine (49, 49)	10.2% (5/49)	52.8% (19/36)	21.9% (7/32)
Actinomycin D (12,13)	2/12 % (16.7%)	72.7% (8/11)	9.1% (1/11)
ATRA (28, 29)	14.3% (4/28)	88.5% (23/23)	0% (0/25)
Bleomycin (93, 95)	4.3% (4/93)	38.3% (23/60)	15.1% (8/53)
Busulfan (31, 31)	6.5% (2/31)	23.8% (5/21)	57.1% (8/14)
Carboplatin (16, 16)	6.3% (1/16)	83.3% (10/12)	0% (0/11)
Cisplatin (92, 94)	0% (0/92)	79.5% (58/73)	18.3% (11/60)
Cyclophosphamide (394,397)	6.3% (25/394)	56.1% (83/148)	16.5% (22/133)
Cytarabine (152, 152)	5.3% (8/152)	53.6% (52/97)	18.4% (16/87)
Dacarbazine (55, 56)	0% (0/55)	51.9% (14/27)	24% (6/25)
Daunorubicin (103, 104)	6.8% (7/103)	65.6% (40/61)	13.2% (7/53)
Docetaxel (20, 20)	0% (0/20)	64.3% (9/14)	7.1% (1/14)
Doxorubicin (411, 414)	3.6% (15/411)	53.4% (79/148)	12.7% (14/110)
Epirubicin (72, 72)	2.8% (2/72)	71.4% (20/28)	10% (2/20)
Etoposide (42, 42)	7.1% (3/42)	48.1% (13/27)	25% (7/28)
Hydroxyurea (60, 62)	3.3% (2/60)	41.7% (10/24)	0% (0/20)
Idarubicin (23, 23)	4.3% (1/23)	84.6 (11/13)	36.4% (4/11)
Imatinib (153, 154)	0.7% (1/153)	14.3% (3/21)	6.3% (1/16)
Interferon alpha (39, 41)	0% (0/39)	27.5% (11/40)	11.1% (3/27)
Methotrexate (79, 82)	11.4% (9/79)	48.9% (22/48)	14.3% (6/42)
Mitoxantrone (17, 17)	5.9% (1/17)	100% (11/11)	40% (4/10)
Nitrogen mustard (30, 30)	3.3% (1/30)	28.6% (4/14)	10% (1/10)
Paclitaxel (30, 31)	10% (3/30)	69.6% (16/23)	22.7% (5/22)
Procarbazine (31, 31)	3.2% (1/31)	26.7% (4/15)	14.4% (2/13)
Rituximab (24, 24)	8.3% (2/24)	58.8% (10/17)	25% (1/4)
Tamoxifen (12, 13)	16.7% (2/12)	75% (9/12)	0% (0/12)
Trastuzumab (17, 18)	0% (0/17)	52.9% (9/17)	0% (0/15)
Vinblastine (72, 73)	1.4% (1/72)	45.5% (15/33)	22.2% (6/27)
Vincristine (219, 221)	8.2% (18/219)	50% (72/144)	11.23% (13/116)
Vinorelbine (14)	0% (0/14)	61.5% (8/13)	0% (0/7)

[a]Differences between the total pregnancies (or conceptuses) for each agent and spontaneous preterm labor are due to the cases for which timing of exposure was not specified.
[b]Includes 5 pregnancies with transient preterm spontaneous labor (Durodola 1979, Li *et al.* 2011, Lycette *et al.* 2006, Ortega 1977) (Meyer-Wittkopf *et al.* 2001).
[c]Preterm birth includes spontaneous and induced vaginal births, and Caesarian-section births.
[d]Data included in this table are based on reported individual infant's gestational age at birth (for preterm birth) and weight at birth (for small for gestational age); studies reporting only group means were not included. Data were also included when the authors did not provide gestational age or body weight at birth, but clearly identified the infant was at term (for preterm birth) or clearly identified the infant was or was not small for gestational age. Births at 7 months of gestation were considered preterm. Births at 8 months of gestation were not tallied because it was not possible to tell if the infants were < or ≥37 weeks of gestation.

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Figure 1. Occurrence (± 95% confidence interval) of major congenital malformations reported in humans possibly attributable to exposure to each cancer chemotherapeutic agent (singly or in combination therapy) during the 1st trimester or 2nd and/or 3rd trimester only of pregnancy. Data are adjusted to remove the major malformations that were not likely caused by 2nd and/or 3rd trimester only exposure to cancer chemotherapy (e.g., Down syndrome, absence of right kidney and ureter, spontaneous mutation for neurofibromatosis, gastroschisis, meningocele, pulmonary artery fistula, rectal atresia, syndactyly of finger or toes, ventricular septal defect, or hypospadias). The left whisker of the 95% confidence interval is truncated at 0%.

5-Fluorouracil	1st	26.7 ± 22.4 (4/15)
	2nd and/or 3rd Only	1.4 ± 1.9 (2/147)
6-Mercaptopurine	1st	5.3 ± 7.1 (2/38)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/42)
6-Thioguanine	1st	33.3 ± 37.7 (2/6)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/43)
All-trans retinoic acid	1st	0.0 ± 0.0 (0/5)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/24)
Bleomycin	1st	6.7 ± 12.6 (1/15)
	2nd and/or 3rd Only	1.3 ± 2.5 (1/78)
Busulfan	1st	15.0 ± 15.6 (3/20)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/5)
Carboplatin	1st	NA
	2nd and/or 3rd Only	0.0 ± 0.0 (0/15)
Cisplatin	1st	0.0 ± 0.0 (0/4)
	2nd and/or 3rd Only	1.1 ± 2.2 (1/89)
Cyclophosphamide	1st	15.9 ± 10.8 (7/44)
	2nd and/or 3rd Only	0.8 ± 1.0 (3/353)
Cytarabine	1st	12.9 ± 11.8 (4/31)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/120)
Dacarbazine	1st	12.5 ± 22.9 (1/8)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/48)
Daunorubicin	1st	5.6 ± 10.6 (1/18)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/82)
Docetaxel	1st	0.0 ± 0.0 (0/1)
	2nd and/or 3rd Only	5.6 ± 10.6 (1/18)
Doxorubicin	1st	8.9 ± 8.3 (4/45)
	2nd and/or 3rd Only	0.5 ± 0.7 (2/369)
Epirubicin	1st	14.3 ± 25.9 (1/7)
	2nd and/or 3rd Only	3.3 ± 4.5 (2/60)
Etoposide	1st	0.0 ± 0.0 (0/3)
	2nd and/or 3rd Only	2.6 ± 5.0 (1/39)
Hydroxyurea	1st	2.5 ± 4.8 (1/40)
	2nd and/or 3rd Only	5.0 ± 9.6 (1/20)
Idarubicin	1st	0.0 ± 0.0 (0/1)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/17)
Imatinib	1st	8.1 ± 4.4 (12/149)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/5)
Interferon alpha	1st	0.0 ± 0.0 (0/21)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/19)
Methotrexate	1st	3.3 ± 6.4 (1/30)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/52)
Mitoxantrone	1st	0.0 ± 0.0 (0/1)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/13)
Nitrogen mustard	1st	11.8 ± 15.3 (2/17)
	2nd and/or 3rd Only	0.0 ± 0.0 0/13)
Paclitaxel	1st	NA
	2nd and/or 3rd Only	3.2 ± 6.2 (1/31)
Procarbazine	1st	21.1 ± 18.3 (4/19)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/12)
Rituximab	1st	16.7 ± 29.8 (1/6)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/18)
Tamoxifen	1st	27.3 ± 26.3 (3/11)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/2)
Trastuzumab	1st	0.0 ± 0.0 (0/14)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/4)
Vinblastine	1st	31.3 ± 22.7 (5/16)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/56)
Vincristine	1st	6.9 ± 6.5 (4/58)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/163)
Vinorelbine	1st	100.0 ± 0.0 (1/1)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/13)